can't do that over here, and there is basically no curative approach to this set of disease. I think most adult oncologists would agree with that now.

[Slide.]

So, this set of data led me to propose, well, we are dealing with two different sets of disease here. That is in the paper, in the handout. One, I call myelodysplasia related to AML because it has features to suggest it is related to myelodysplasia. It has monosomy 7, 5q-,+8, has background dysplastic morphology. When it enters remission, it often looks like MDS, and the disease shares multiple features that I just described with AML following overt MDS.

[Slide.]

And given this age incidence of MDS and the fact that 10 to 40 percent of these are going to progress to AML we know, I think, that is this set of disease.

The other set is the set with a median age in the 30s, and there is one important additional point to garner from this slide.

[Slide.]

That is, this is the age incidence of a disease at least that can be explained by a

multi-step, random multi-step pathogenesis, for example, colon cancer.

An age incidence like this was used to predict that colon cancer has a random multi-step pathogenesis, and this has been largely borne out in studies coming from Johns Hopkins, for example, and other institutions over the last decade.

So, this doesn't prove a random multi-step pathogenesis, but it does have implications about the pathogenesis, whatever it is. Whatever the pathogenesis ends up being has to explain this age incidence.

If this is, for example, a multi-step pathogenesis, what is this, and this cannot be a random multi-step pathogenesis, it can't, because that gives you this curve.

So, without even knowing what the pathogenesis of either of these sets of disease is, we can say, I think with some assurance, the pathogenesis has to differ in these two sets of disease, and this has to be some fairly simple rate controlling pathogenesis.

For example, in some cases, this could be a recurring translocation even if the recurring translocation is insufficient to explain the

disease. It can still be the rate-limiting effect, and once you get that, other events happen, and you then develop whatever disease is characterized by that translocation.

[Slide.]

So, how does the FAB--I have given you a model here of AML--how does the FAB classification work with this model? This is a very simple study we did in SWOG comparing patients less than 50, who should be predominantly true de novo AML, and greater than 50, who should be predominantly myelodysplasia-related AML.

I think you can see the historical approach abjectly fails to spot these differences, which I would submit are much more important clinically and biologically than whether the case is myeloblastic leukemia with minimal or more differentiation or myelomonocytic leukemia or monocytic leukemia, for example

So, the historical approach totally misses these very important clinical and biological discriminants, so from my perspective, although this is very useful for pathologists and morphologists for recognizing the morphologic variants of AML, for diagnosing AML, at that point

it becomes substantially irrelevant, and we need another classification, which I have proposed.

[Slide.]

Let me just use promyelocytic leukemia to illustrate the true de novo subset. This is a classic picture for promyelocytic leukemia, I won't go into the details, but hypergranular cells and lots of Auer rods, for example, very characteristic.

[Slide.]

It has a recurring translocation, ignore this down here, it is obsolete, but the picture is correct, the 15;17 translocation.

[Slide.]

Genes have been cloned, PML and chromosome 15, RAR-alpha and chromosome 17. We have identified that these both appear to be important maturation regulators although especially for PML, we don't understand quite what it is doing yet.

We have characterized these translocations. There are three different translocations that occur. Extensive work is going in the study and other de novo subtypes of leukemia.

[Slide.]

We did an extensive analysis combining cases from St. Jude and the Pediatric Oncology Group, pediatric patients, and the Southwest Oncology Group, adult patients, and we basically couldn't see a difference in the two subsets from the standpoint of morphology, cytogenetics, and molecular testing.

These are the participants in the study. Of 71 cases that had confirmed 15;17, 68 were acute promyelocytic leukemia. I will point out, though, that 3 were not acute promyelocytic leukemia, and this type of case still responds to all-trans-retinoic acid in the literature, and there were other cases that had promyelocytic morphology, but lacked the 15;17. These cases were entered in the first U.S. ATRA study because entry was based on morphology, not on genetics, and those cases do not respond to ATRA.

So, I would suggest that for this morphogenotype that appeared at first to corroborate the historical approach to AML classification, that, in fact, it is the genetics that are important, it is not whether they are actually promyelocytes or not. That is simply a secondary feature of the genetics in most cases.

[Slide.]

So, this leads to two different models for leukemia. For the true de novo subtypes, there is some kind of initiating event that starts cells growing in a transformed state.

This doesn't say whether there was one event or several concomitant events, but it appears that once you transform a cell and perhaps escape immune surveillance, these cells just start dividing, 1, 2, 4, 8, 16, 32 until you get to about 10^{12} cells. The only difference there is you now have a tumor burden that gives you clinical symptoms, but you have had the disease for a long time. If you can spot this disease early, you should treat it early, as soon as you are sure you have an uncontrolled proliferation with one of these characteristics, that is leukemia.

So, to speak of, as is known in the literature, myelodysplastic syndrome with favorable cytogenetics meaning disease with an 8;21 translocation and a low blast count, 10 percent less, no, that is not myelodysplastic syndrome, that is AML, and you just were lucky enough to catch the patient early. It is still true de novo AML, and it should be treated as such, and that

same story is true whether you are dealing with an adult patient, a pediatric patient, or an elderly patient.

If an elderly patient has one of these diseases, the disease responds the same to the treatment regardless of age. The host may differ, but the disease is the same.

As opposed to that, the other set of disease is very complex and is receiving very little study right now even though it is half of AML. These cases are vastly under-represented in adult oncology trials because they are very difficult to treat, the treatment is very unsatisfactory, but also, very little is being done to try and ferret out the biology of these diseases.

We have no idea in most cases what the initiating events are. There are some clues from some pediatric syndromes, Fanconi's anemia develops this set of disease, severe congenital neutropenia, Kostman's syndrome develops this set of disease. We know that some drugs cause this set of disease, other drugs cause this set of disease, so epipodophyllotoxins tend to cause in particular where to go.

MLL/AF9, for example this set of disease, MLL translocations, alkylating agents, various cross-linking agents cause this set of disease, but once we get past that point, we have little idea what the pathogenesis of this set of disease is.

We know there are multiple steps. We can define a low-grade MDS, a high-grade MDS. We can probably define some events that happen when this progresses to leukemia, like EVI-1 dysregulation in RAS point mutations, perhaps C-fems point mutations.

But what happens over here and what causes all these just remain a mystery right now.

[Slide.]

So, let me then close. I have given you my assessment of the historical approach, a different approach that I have proposed, published in 1996, that we use now in the Southwest Oncology Group and to some extent in the Children's Oncology Group, we are evaluating these.

This is the World Health Organization, new World Health Organization classification of AML. I sit on the subcommittee. Other members of the subcommittee are John Bennett of the FAB group, George Flandron of the FAB group, Estelle Matutes,

who works with Daniel Catofsky in London, of the FAB group, Richard Drumming, the chairman, and myself, and we did not reach 100 percent agreement, and ended up with a compromise, but I will present the compromise.

There are four subsets in this classification, AML with recurrent translocations, which corresponds approximately to my true de novo AML; AML with multilineage dysplasia, which corresponds approximately to my MDS-related AML; AML and myelodysplastic syndrome therapy related, and I have described that there are, in fact, iatrogenic models of these two unfortunately, and that is what this group is, alkylating agents for this set and cross-linkers; and epipodophyllotoxins and some other drugs for this set, and then AML not otherwise categorized, and I will come back to that in a minute.

[Slide.]

So, this is some of the recurrent cytogenetic abnormalities. For reasons I don't completely understand, we didn't list all of them, but we just listed these four, but nevertheless, it is basically true de novo AML in my classification.

[Slide.]

Acute leukemia with multilineage dysplasia was limited to these two settings. I would have included AML with monosomy 7, trisomy 8, complex cytogenetics.

[Slide.]

And MDS and AML therapy related.

[Slide.]

And before I show the next slide, one directive we were given was this is the World Health Organization classification, it is not just the United States, Western Europe, and Japan classification, so we had to create something that was to some extent applicable around the world where they don't have access to many of the more refined technologies that we use, so a fourth category was added, and this is basically a slightly refined FAB classification of AML.

So, what we have then is a classification based on two different sets of ideas, attempted to be melded into one classification, but this is the genesis of WHO classification of AML.

[Slide.]

I have one more slide. This is Dr. Bernstein's slide, again. I will ask Irv--are you there, Irv?

DR. BERNSTEIN: Yes, I am. Can you hear me?

DR. HEAD: Yes, we can. Would you care to comment on your PMA 676 inhibition slide?

DR. BERNSTEIN: Maybe I will just make two points. The first is that I agree with what you said. But, given that, it is clear that in the future we will be looking at comparability between adult and pediatric disease even more based on genetic abnormalities.

I would just want to point out that although we don't know the complementing events that occur with known translocations or the events with leukemias, we are rapidly learning mutations, for example, cytokine mutations.

One has to believe as new drugs are being developed that will target pathways that are affected by these mutant cytokine receptors, that one would really define leukemias between adult and pediatric based on the lesion of the particular molecular pathway.

So, although we need a classification, in the future, one way of defining will be abnormalities of the pathway that new drugs will specifically target, and that is clearly an area of

interest.

In terms of functional effects of drugs, the one thing I would want to point out is that in the development of Mylotarg, this is the gemtuzamab ozogamicin or the anti-CD33 antibody calicheamicin conjugate, that, in fact, was developed based on the notion that for at least most pediatric and young adult patients, disease was unipotent, that is, usually limited to granulocyte and monocyte differentiation as opposed to more frequently seen in the elderly patient where there is multilineage disease.

So, based on that concept that was worked out by Phil Fialco, looking at G6 PD polymorphisms at a clonal marker, there was a notion that precursor cell involvement may be greater at the committed myeloid stage for patients with unipotent disease, and it was based on that, that we thought that targeting committed precursors would be useful with anti-CD33 antibody.

I think the important point is that since that disease was a disease of younger adults and pediatric patients, we, in developing this conjugate, selected linkers based on their ability to kill leukemic colony-forming cells in vitro from

pediatric and young adult patients, younger than 60.

In fact, if you have the slide up, what you can see is that we selected a linker to join the drug and the antibody, such that the killing that we observed was, in fact, greater for pediatric patients than for adult.

So, here is an example where a drug was developed on a concept that applied to young adults and pediatric patients, that was, in fact, most optimized for pediatric patients and really for evidence of functional information about a drug that probably should have been tested in kids first and adults second, but obviously, it was done the opposite way, so I think that best made the case for testing in pediatric disease, as well.

Otherwise, I have no other comments to make unless I can answer any questions.

DR. HEAD: Thank you, Irv.

I agree completely with Dr. Bernstein's comments, and I don't mean to minimize in my presentation the importance of secondary events in these leukemias, but what I have tried to present is an overview model, an overriding model to allow us to synthesize data in the future.

In my overview in which I attempt to create a different structure to look at leukemias, I am not saying secondary events after an 8;21 translocation or a 9;11, et cetera, are not important, and may actually have therapeutic benefit or clinical relevance, but I think to get to that point, we first have to get to the point of accepting these are each different diseases that we need to look at separately.

I would just make one last point, and that is, in my estimation, to make progress in treating these diseases, we are going to have to admit that these are multiple different diseases, 9;11 AML is not the same as 8;21 AML. They may have different chemotherapy response profiles, and they are going to certainly have different biological response profiles, and we are going to have to figure out how to do studies for specific genetic diseases.

I have suggested that at least there is a basis for treating the specific genetic diseases very similarly or identically in young patients versus older patients.

Discussion

DR. SANTANA: Now we have time for direct questions and discussion with David's presentation

and Dr. Bernstein's comments.

I want to have a brief comment, David. One concern that I have with this WHO classification is that that last category seems to be the excuse category, that you can't do the cytogenetics, you don't have that other information, and therefore, you fall back on the old principle of using morphology, and the concern is that if this classification is used widely for study design, then, you are really going to be into trouble, because you are going to have patients that are not truly representative of the best.

Do you see what I am saying, that you are going to be then having information on some patients based on trial design that are specific for a cytogenetic issue, but then a great proportion of those patients in which you don't have that information for whatever reason, how did those patients get treated, and what do you learn from those patients.

DR. HEAD: I agree with that point completely, and think the last category should only be used when a sincere attempt for studies in the United States, after a sincere attempt to place the patient in the first three categories fails, that

the patient does not have a recurring translocation and you can't decide which category to place the patient in. I agree with you completely.

DR. SANTANA: Dr. Arceci.

DR. ARCECI: A couple quick comments, I think, and actually questions.

One is the idea of the hematopoietic stem cell leading to a leukemic stem cell in this situation. I know certainly Irv and I, in our strategy group, have discussed this at length, but in fact, in some of the data that is occurring, maybe, it is not, in fact, the stem cell that is either further back or further forward with the exception possibly of APL, but it is really what lesion occurs in that stem cell that leads it into your two categories.

So, it is not how far back you go in lineage necessarily, but it is what lesion you acquire in that setting. I would be curious to know what you thought about that because I think it has implications in terms of your last point in terms of genetic targeting.

The other question is can we, are we at a point where we can define potential therapies or classification just on the molecular genetics of

these lesions? For instance, TEL was originally cloned out of a myeloproliferative disorder, not ALL, where it's a good prognostic feature, and I think that if you just had a PCR result on a chromosome 12 TEL-related event, and you didn't have anything else, I think you could make the wrong therapeutic decision based upon that molecular lesion depending upon what cellular context that lesion took place in. It is really a question. I don't know the answer.

DR. HEAD: From the standpoint of the first question about how primitive the stem cell is, I think in myelodysplasia-related diseases, the stem cell involved has to be at least a multipotential myeloid stem cell because the cases have multilineage dysplasia.

So, if you have dysplastic megakaryocytes, granulocytes, and erythroid cells, the lesion must be in their precursor or more primitive. For the true de novo cases, as more data become available, it is not clear how primitive the stem cell involved is.

Promyelocytic leukemia may be an exception. It appears to be a fairly committed myeloid stem cell there. The 8;21 translocation

appears to have and also in a multipotential myeloid stem cell, so can you speculate, well, what are the differences, and I can only speculate.

I speculate that the differences in the underlying pathogenesis of the process, that actually the real unifying feature in MDS and that sort of disease is that they are a mutator phenotype and get progressive complex genetic damage that leads to leukemia, but that is speculation.

DR. BERNSTEIN: If I could add one point on that, Bob is absolutely correct that we really can't tell where that lesion occurs. I think what the experience speaks to is either where the lesion occurs or where unregulated expansion of the cell occurs, and that would be where, whatever this lesion is, would affect the context of signaling in that cell.

So, in fact, when John Dick's animal models claim that early, very primitive precursors are involved in the leukemic process, that is probably correct. The differences probably are that the unregulated expansion of precursors doesn't occur until a particular stage of differentiation of multipotent or unipotent cells.

So, in a sense, both answers are correct, and the differences are probably quantitative differences in the involvement of the earlier cells. It is not clear how to translate all of this, but at least it is a concept to think of.

DR. ARCECI: And what about Down's syndrome and infant leukemia, could you guys comment on that because those may be exceptions to what we are talking about.

DR. HEAD: I will comment first and then if Irv has comments, Down's syndrome is a perplexing exception because it appears to develop, has a high incidence of AML, and the AML is often preceded by what appears to be myelodysplastic syndrome, and yet, in total contrast to all the rest of myelodysplastic syndrome and MDS-related AML, AML in Down's syndrome has an outstanding prognosis, and I don't know how to explain that.

The second, infant AML, I didn't mention infant AML, but it is very interesting. AML, less than one year of age, has a different set of recurring cytogenetic features than AML after approximately one year of age. Less than one year of age, well over 50 percent of AML has an MLL translocation, and after one year of age it reverts

to the approximate frequency throughout the remainder of adult life, which is on the order of 4 to 5 percent.

There is a second subtype of AML, megakaryoblastic leukemia with the 1;22 translocation that appears to be confined to patients less than one year of age.

So, there have some interesting biological implications, also suggests some interesting pathological implications that these translocations are not just stochastic events happening by chance, there are factors influencing their happening even though we don't know them, and whatever those factors are appear to change from the in-utero environment to the ex-utero environment.

DR. ARCECI: But the MLL of infants, would you target that the same way you would target the MLL of the older child in terms of this conference?

DR. HEAD: And I don't know the answer to that.

DR. SANTANA: Dr. Boyett.

DR. BOYETT: A question for Dr. Bernstein. I am sure you have mentioned it, and I missed it, but in your data for the CMA-676 analysis where you had adult and pediatric AML cases, what was the

defining genetic defect, and was it the same in both samples?

DR. BERNSTEIN: That actually was not looked at in those samples, and we actually don't know the impact of genetic defects on the effectiveness of the conjugate.

DR. SANTANA: Dr. Borowitz.

DR. BOROWITZ: Could I ask Dr. Bernstein, do you have any comments on Dr. Arceci's previous questions?

DR. BERNSTEIN: The only thing I could say is that MLL defects in infant leukemia, you know those are interesting abnormalities because they clearly arise in utero, they can be transplanted in twins from one to the other, so they may be single events leading to that leukemia.

It is interesting that the prognosis of older children with AML is quite different, so one might speculate that there are differences, the context that arises at a later time, but obviously, there is something we don't know very much about except the striking difference in prognosis.

DR. BOROWITZ: Yes, sort of a comment and maybe to comment back, it picks up on something you said, David, about thinking about every one of

these diseases as a unique entity.

I don't in any way want to minimize what we have learned or the importance of understanding the mechanisms of specific translocations and how downstream events may lead these to leukemia, but when you step back a bit and talk about therapy, and talking about designing targeting agents, it seems to me that if that is the overweening strategy that one uses for treating leukemia, that you wind up with a bunch of orphan drugs.

I think the contrast between ATRA as a therapeutic agent and Mylotarg as a therapeutic agent, I think are striking because Mylotarg looks at some common phenotypic property that all of these leukemias, I won't say irrespective of their genetics, but likely lumping several of the similar genetic lesions end up sharing an important phenotypic property.

I think in terms of rational design for therapy, we are all, as we sort of explode our knowledge of the detailed mechanisms of leukemias, it is always attractive to look towards very specific genetic targets, but I think we should be trying to look downstream in commonalities of these things because I think over the long haul, we will

wind up with more effective agents.

DR. HEAD: That is a very good point, very practical.

DR. SANTANA: Dr. Hirschfeld.

DR. HIRSCHFELD: I had a very specific question to Drs. Head and Bernstein.

There is some speculation that the MLL translocations--and it relates in a way to Dr. Arceci's comment, too--the MLL translocations in infants may be similar to the type of translocations seen secondary to exposure to cytotoxic therapy.

I wanted to hear your sense as to the credibility of that speculation and whether one should consider these types of leukemias to be in the type of classification scheme that Dr. Head is discussing, to be in the same category.

DR. HEAD: Irv, can you comment on that?

DR. BERNSTEIN: I can say there are epidemiology studies asking about exposure of mothers to topo II inhibitors, and I can't really comment on that.

Molecularly, can anybody comment whether the breakpoints are precisely the same or different between the two entities?

DR. SANTANA: Dr. Arthur?

DR. ARTHUR: I know that Dr. Rowley was conducting some studies particularly into that, thinking of the breakpoints in the treatment-associated patients might be different, but I don't know if that has been definitively decided.

DR. HEAD: The extent of my knowledge, which I have been remembering while I asked people to speak, Dr. Rowley's group, and also Dr. Peter Domer, have looked at the specific intronic break in post epipodophyllotoxin AML versus infant AML to see if the breaks were in similar portions of the intron, and I believe the conclusion was although it was an attractive hypothesis, that maybe there were topo II inhibitors in utero that were leading to this secondary MLL disease.

I believe the conclusion was the breaks in the infant disease were at different sites in the introns and the breaks post epipodophyllotoxin, which then suggests that at least infants versus secondary epipodophyllotoxin MLL translocations may have a different pathogenesis even though they both result in similar translocations.

DR. SANTANA: Dr. Poplack.

DR. POPLACK: I was just going to make a comment in follow up to Michael's statement about the search for common downstream events.

I think that is clearly the ideal, but it actually may be that as we search downstream, we find less commonality and more uniqueness, and if so, perish the thought, we may be talking about AML, for example, as a disease that ultimately is optimally treated by 35 different specific targeted approaches and a clinical trialist's nightmare.

So, yes, we always have to look for the common, but we may have to be prepared for the fact that for us to get to 100 percent across the board may require a totally different paradigm than we have used in the past.

DR. BERNSTEIN: Could I make a comment on that?

DR. SANTANA: Yes.

DR. BERNSTEIN: You know, it is correct that if one looks at the computations of mix and match, for example, 8;21 plus a second or a perhaps third mutation, that one will have a myriad of diseases, but, you know, if one looks, for example, at FLT-3 tandem repeats, you have a substantial percentage of patients who have this, where one

really could envision targeting specific lesions where the complementing lesions in a particular leukemia may be very different.

So, I don't think it is far-fetched in one set of circumstances in development of very specific drugs, that one really could define large groups that may benefit.

As far as looking at the whole of leukemias, it is still possible that for very powerful cytotoxic agents that kill in general, that the differences, the discriminators between adult and pediatric may be the opportunity to develop resistance mechanisms, for example, the substantial differences in MDR in patients at diagnosis, you know, younger versus older.

I think one, rather than limit oneself with classifications, really needs to ask some very specific questions about if it is a very specific targeted therapy for a pathway, one could look at that pathway independent of other events, and if it is a general cytotoxic agent, then, one could not only ask molecular specific, but needs to pay attention to what might be a resistance mechanism that may be common or dissimilar between pediatric and adult.

DR. SANTANA: What is likely to happen, though, my own simplistic view, what is likely to happen in the next couple of years is that as the fields evolve or complement each other, that we are not going to abandon the traditional cytotoxic, neither are the sponsors, and the new specific molecular targets will be identified, drugs will be developed or biologics to that, and they will be complementary to a certain degree to what we already do. I mean that is my own simplistic logic here.

Bob.

DR. ARCECI: I would actually hope that we do abandon them and that--you do, too, I know you do, Vic--

DR. SANTANA: I just don't know, I don't have enough information.

DR. ARCECI: But in some respect we may have a different backbone, such as non-genotoxic, cytotoxic agent, such as the farnesyl transferase inhibitors or monoclonals, those approaches to cytoreduce generically, but then I think, as David pointed out, in terms of what you are saying, Michael, and the specificity of these lesions, I think that as you look further downstream in terms

of signal transduction, for instance, you are going to find more commonalities that are going to also be more common to normal hematopoietic and other cells in the body.

So, for instance, internal tandem duplications of FLT-3, will induce certain signals downstream. A different mutation in the c-kit receptor will also initiate and up-regulate those downstream signals, for instance, STAT-3.

So, if you target the STAT-3, you are going to affect normal cells potentially, and I think that is where Irv was talking in terms of drug resistance. Mostly normal cells are going to be more resistant.

However, the issue here is if you target FLT-3 with a specific drug, you will more likely affect those cells with less toxicity to normal tissues, whereas, that may not work in those with c-kit mutations.

So, I think it is going to be a balance, and if we have to, in a sense, put clinical trialists out of business by going to more molecular approaches, so be it. I think we would all be unhappy with that if we ended up that way.

DR. SANTANA: Charles.

DR. SCHIFFER: To get back to why we are here, if we have a drug that for some reason we think targets 8;21 or MLL, I would propose that that drug should be developed, particularly if it is a targeted drug, simultaneously in adults and children, and possibly in the same trials. I mean that is what you want out of this, I think.

As Sharon said, there is certainly precedent for this. The APL trial is a very good example. These are relatively uncommon phenotypes, et cetera.

One of the nice things about the highly targeted drugs so far is that you didn't need statisticians, you needed two patients, and you knew you were on to something, and the subsequent trials were to determine how best to use the drugs, and I would suspect that if you develop small molecule inhibitors of many of these discrete, necessary, but not sufficient mutations, we are going to see the same thing.

But even if there is a difference in infants with 4;11 or MLLs, well, then, it will fall out. You know, when you have such a hypothesis and a discrete target with good in vitro data, then, include them all and see what happens, and build on

the APL model and do it quickly, and I think that pharmaceutical companies should hear this also.

DR. SANTANA: Dr. Borowitz, you had a comment or question?

DR. BOROWITZ: I just sort of wanted to return to my comment that has elicited some response, and I didn't mean to suggest that when I say look at downstream commonalities, that doesn't mean that I am suggesting that we go back to conventional chemotherapy strategies.

The idea is if we focus just on the sort of cytogenic translocation, and not the downstream common pathway elements, I think we miss an opportunity to do more intelligent design, and they could either signal transduction pathways or apoptosis pathways, or things like that, and I think we can't get too sucked into our advances in classification and assume that that is going to be the only answer to our therapeutic approaches.

Questions to the Committee

DR. SANTANA: If there are no further comments, I want to go ahead and start addressing the questions because the FDA has posed some questions for us that we need to advise them on. I think that we have covered some of it kind of here

and there during the discussion, but I want to be more formal and go through them.

My first comment is I don't think you are asking us to endorse one classification system versus another with the first question, you just want some general comments in terms of if we were to use the FAB classification, how that could potentially be used in children and adults, and so on, and so forth.

DR. HIRSCHFELD: Right.

DR. SANTANA: So, let's try to deal with the first one then.

DR. HIRSCHFELD: May I just comment that the intent is not to make one point of view "the official FDA point of view," but rather just to elicit comments, and we are not asking for votes on any of these questions, but just would like the issues that the questions raised aired.

DR. SANTANA: The first question is - For myeloid leukemias and myelodysplastic syndrome: A. Should the FAB classification be used as a basis for relating adult and pediatric myeloid malignancies? If you think not, what other criteria should be used?

Dr. Arceci, do you want to start

addressing that?

DR. ARCECI: I think that David and Michael would agree that that is probably an inadequate classification to make those decisions on. I think you would have to take it to the next level, as I think David and others have pointed out. So, I would say no.

DR. SANTANA: David, do you want to comment on that or follow up?

DR. HEAD: I agree completely. That was the point of my talk. I think we need to move beyond that. I have suggested two broad groups that I think are more relevant. To the extent we can define those two groups, I think we should use those two groups.

When we can define groups more specifically, for example, t(8;21), t(15;17), I think we should use those.

DR. SANTANA: So, what you are saying is that the corollary note to that answer is that the other criteria that should be used, should be some cytogenetic criteria or molecular criteria?

DR. HEAD: Should be cytogenetic, molecular, if such are available. Those are not necessarily available for myelodysplasia-related

disease because 40 percent have normal cytogenetics, for example, and we don't know what the molecular events are in this set of disease.

So, in some settings, it needs to be based on other parameters, for example, history of MDS, history of drug exposure, background dysplasia, which is used in the WHO classification, if you can do it and corroborate my synthesis of the data, clonality, if hematopoiesis, may be something that could be used, at least in females, et cetera.

DR. SANTANA: Sharon, you had a comment?

DR. MURPHY: I think David is being very modest. I think he has presented a wealth of data, and it has been now widely shown the FAB classification should not be a basis for making decisions.

The criteria, at least for starters, should be this broad separation, I think, between true de novo AML, characterized by these chimeric proteins and specific translocations versus the myelodysplastic-related AMLs for a starter.

I applaud his contributions and the fact of getting us all to think about a new way of thinking about AML. I mean I have decided I am going to stop teaching the FAB classification is my

plan.

DR. SANTANA: Dr. Bernstein, do you have any comments on this?

DR. BERNSTEIN: I agree with those last comments.

DR. SANTANA: We can hardly hear you. You said you agree?

DR. BERNSTEIN: I agree with those comments.

DR. SANTANA: Any other comments to subpart A?

Subpart B. What general principles could then be used to relate myeloid malignancies in adults to myeloid malignancies in children?

Charlie, do you want to address that?

DR. SCHIFFER: I think the cyto and molecular genetic findings when they are homogeneous. The problem is that there are large numbers of patients who fall in between or who don't have such findings, and there the results in adults and children are approximately the same and equally poor.

It is going to be difficult to target if you don't have a chimeric protein unless, in fact, something like the FLT-3 represents a target, and

you might be talking in this arena about a new cytotoxic, whether it be a semi-targeted one like a CD33 antibody or whether it might be a new drug, although I can't think of the last new drug that has come along for AML in the last 30 years.

But I think it is this group of patients in the middle who exist for both adults and children, i.e., you don't have one of the obvious cytogenetic classifications, they are not obviously myelodysplastic. In adults, it may be as high as 30 or 40 percent of patients, it may even be a higher percentage in children.

I think the relevant question there is if some new drug comes along that gets tested, for example, in relapse disease, which Mylotarg has set up a nice target for a new drug in relapse disease, and then gets accepted because it appears to have activity comparable to or better, should the same results apply in adults and children, do you think the results would be the same.

I would think they probably would be the same, but it may be that such trials would not be conducted simultaneously in adults and children, so then should this be a mandated area, for example, because this is a very substantial fraction of

patients with AML in both age groups.

DR. HEAD: Could I make one comment affirming what Charlie just said, and that is, that we have no definitive way of spotting MDS-related disease, and we are not sure we have definitive ways of spotting all true de novo AML, and I will just use 12;21 ALL as an example, can't be spotted cytogenetically, you have to do molecular testing to spot it, and if you don't know to look for it, you never see it, and there may be similar categories of true de novo AML that are yet to be defined, and we don't have any specific test we can do for MDS-related disease.

We can only look at secondary features if they have developed monosomy 7, trisomy 8, complex cytogenetics, but these are all secondary events, and they don't necessarily happen in each patient. Forty percent of the patients, we can't figure out where to put them in these two categories right now except by age, and that is not the best way to do it, but that is all we have got.

DR. SANTANA: Dr. Borowitz.

DR. BOROWITZ: I think there is a principle at stake here, that if we sort of turn the question around and say under what

circumstances would it be legitimate to have a waiver, and not apply the Pediatric Rule in AML, I think the cases where they share a common translocation of one of the true de novo AMLs, it is easy to say, but it is this intermediate group that is more difficult.

My bias, and maybe this is what Charlie was saying, is that in these cases where you can't clearly demonstrate that it's MDS-related AML, and therefore, a disease that is much more likely to be seen in adults than childhood, you should err on the side of saying that the leukemias are the same unless you have compelling evidence to suggest that they are different.

I think that this opens up a much larger envelope of cases where you can start looking at common therapies than if you just restrict it to those sets of diseases where you have demonstrably identical translocations.

DR. SANTANA: Sharon, you had a comment. I know you have had your hand up for a while.

DR. MURPHY: That's all right. Actually, we are all kind of converging, I think. So, I would answer the question the general principles would be, one, if they clearly share a specific

molecular marker, translocation, or whatever, then, they are the same, like APL, RAR-alpha, AML, that is the same in adults and children.

Then, there is the ones that don't clearly share anything, and are the great NOS, otherwise unwashed, broad category of AML that we all face, and a drug is targeted to AML, not a specific maybe molecular designer drug, but a general AML like Mylotarg or something else down the line, then, they should also be considered the same.

I am having trouble thinking of where they are clearly different unless it's an entity that occurs only in AML in children, like megakaryoblastic leukemia and Down's syndrome, which is, you know, angels on the head of a pin here, and/or something specific, can you think of a kind of AML that only occurs in adults.

I mean some of the more myelodysplastic forms might be granted a waiver, because myelodysplasia is so rare in pediatrics, I mean it is just impractical to try to mandate studies. That would be my answer.

DR. SANTANA: Dr. Waxman.

DR. WAXMAN: I just want to expand on what you said, that the malignant phenotype may be the

same despite not having the same abnormality in translocation. So, I think if a drug is being targeted to a specific malignant phenotype, such as an amplified c-myc, or an over-expressed BCL-2, or you are trying to overcome MDR, that principle should hold right across the board whether it is an adult or a pediatric case, if you are targeting a drug that way, and it should be similarly tested as can you--back to leukemia--overexpresses that, you are going to attack that, actually, I think it should go across the board.

DR. MURPHY: But could you clarify, though? I mean the examples you used, for instance, overexpression of BCL-2 is not something we see in pediatrics.

DR. WAXMAN: No, I was using that as an example that if it's not BCL-2, then, it's BFLA-1, so that we know more and more about what we are trying to attack downstream as it was brought up before. It may not be a primary event, but a secondary event of transformation, and so that is a target, and it goes across the board.

DR. SCHIFFER: Actually, BCL-2, not mutated, but BCL-2 is overexpressed in many, if not most, AMLs, and might actually represent a target

which would go across age groups.

DR. MURPHY: I was thinking with the lymphomas.

DR. SCHIFFER: I understand.

DR. SANTANA: Dr. Pazdur, you had a comment?

DR. PAZDUR: I wanted to follow up on something that Sharon was mentioning for clarification. Bringing this down to what is going on now in drug development where many drugs are not being developed for a specific target, but many times we are seeing conventional cytotoxic drugs, for example, me-too anthracyclines, me-too ara-Cs, et cetera.

If somebody was developing a drug, for example, for refractory AML without a specific molecular marker at this time, should we exert our regulatory authority in mandating that drug to be examined in pediatric AML?

DR. SANTANA: Comments? Dr. Borowitz.

DR. BOROWITZ: Just a comment about that, and I think it does reflect part of the problem between how drug development works and what refractory AML is. I mean I think, as David pointed out, myelodysplasia-related AML is very

highly resistant to conventional chemotherapeutic agents, so in a protocol for refractory AML, in the typical adult population, you would expect that population to be highly over-represented with the kind of AML that doesn't occur in children.

So, my own bias is if that is the target for drug development, that may not be the most fruitful place to invoke the Rule.

DR. PAZDUR: I am just giving that example because in adult indications, most of the drugs are developed in refractory diseases and then brought forward, but the intention usually is to take the drug then and develop it further in adults in that first-line setting, et cetera.

But the point that I am trying to get across is that yes, these molecular markers are being evolved and therapies are being evolved against them, nevertheless, in a real world situation, we are still dealing with conventional cytotoxic drugs and how should we look at those drugs also.

DR. SANTANA: Dr. Reynolds.

DR. REYNOLDS: I would agree with you, and I have heard several comments here that basically is arguing for lumping rather than splitting on

this, and I think that if you are using general cytotoxic agents, what we haven't heard on this in terms of all of the cytogenetics and molecular markers that have been able to differentiate between survival outcome in these groups, we haven't seen any data that has been distinguishing the response rates in Phase II trials.

I think if you are taking a new molecular entity forward, especially a general cytotoxic agent, the real question is could you on any of these data presuppose that the response rate would be different between pediatric and adults, and I don't think that would be the case.

So, it would seem that we would be better off to apply the Pediatric Rule and obtain that data and that agent rather than have the agent languishing while we are waiting to figure out what the exact molecular relationships are.

DR. SANTANA: Dr. Arceci and then Dr. Smith.

DR. ARCECI: The one area that is somewhat confusing here, though, if we co-develop, you know, "rudolphomycin," or whatever one is coming down the pike, the issue in my mind is where do we start Phase I trials in pediatrics if we don't have any

information prior to starting those trials in terms of dose finding, and it is a thing that we have worried about in pediatrics because of what I think Susan brought up earlier in terms of benefit.

Although most Phase I's don't result in long-term benefit necessarily, we have probably spared enrolling some children at very, very low doses based upon the fact that we start at a dose 80 percent of the adult.

I would be curious, I think it's an important area, if we are going to recommend mandating co-development of some of these agents, then, we probably need to think how we are going to do that in pediatrics.

DR. SCHIFFER: Why is that less of an ethical problem in adults?

DR. ARCECI: Because they can give consent, a pediatric patient cannot, and it really goes back to McIntyre's, you know, whose justice, whose rationality.

DR. SANTANA: I mean you could turn it around and say, for example, for biologics, MTD dosing is completely irrelevant.

DR. ARCECI: I think that gives us a huge opportunity, but for the other agents, I think, I

am not sure how we do this or how we deal with it.

DR. SANTANA: Malcolm.

DR. SMITH: To Rick's question about what do you do with another cytotoxic, it gets back to the issue of the need for a dialogue. There are a limited number of Phase II studies that can be done in recurrent AML, and it may be that the best thing available is a new anthracycline, you know, who knows, but it may be that that is competing with three or four other agents that have not been tested before for their distinctive mechanism of action.

So, a mandate to study the former may, in fact, now contribute to overall development of new therapies for AML.

DR. SANTANA: Good point.

Dr. Boyett.

DR. BOYETT: Similar to Dr. Borowitz's comment for perhaps a different reason, I think I would like to be a bit more conservative about applying the mandatory rule at this point in time, and maybe restrict it to those things where we know we have some genetic definitions.

In the future, the groups of AML patients that we cannot now distinguish because of some lack

of genetic markers, I think we will have techniques in the future.

I would be concerned about mandating it to the broad category and then having studies come out that not be productive and actually killed it, when, in fact, if we restrict it to those where we have some hope of some targeted intervention where we really believe that perhaps the adult and the childhood AML is the same, I think we need to produce some positive results to build upon.

DR. SANTANA: Yes, I think this goes back to the issue of a conversation that has been occurring in terms of prioritization and dialogue. I mean at some point, a community, whoever that community is defined, FDA, NCI, cooperative groups, individual sponsors, needs to decide what the priorities are because we are not going to be able to test everything that we want to test.

I think those priorities have to be established through a dialogue, and not through individual sponsors or individual groups.

Steven, you had a question or a comment.

DR. HIRSCHFELD: I think every comment is a question that can be a question unto itself, to take off on Dr. Arceci's commentary.

Well, I wanted to put out a speculation, and again this is not a formal position, it is just a speculation for discussion, that to interpret the word "studies" may not necessarily mean clinical studies, and the speculation I would want to propose is if one says studies should be mandated, and we had--and this is another supposition--an effective screening mechanism for looking at inactive drugs, that is, if there was a method where we had with a great deal of certainty lack of activity in the screening method, whatever that may be, correlated with lack of clinical activity, then, we might consider asking for studies in the screening method, because I think the data to support that because there is in vitro activity, there will be clinical activity is much shakier.

But if there was a possibility of having negative data translated into negative data, then, that might address some of the priorities and some of the circumstances where one isn't sure.

DR. MURPHY: Since you want to be provocative, I am trying to imagine what are you thinking, and what screen possibly could be validated, and so I am guessing, is he thinking, you know, the current trendy gene expression

profiling with chips and stuff, and the hypothesis, you know, increased expression, it might work or not.

I don't think we have a shred of evidence to go forward on those kinds of screens in real human disease and responses to treatment, and I would worry about using something that is not validated in a pre-clinical way to mandate rules myself. Maybe you would like to tell us what you are thinking. You must have something you are guessing at.

DR. HIRSCHFELD: Sure. It would be absolutely contingent on some validation. So, I will take an example, not from AML, because I think that is much harder, but if we go to, let's say, the solid tumor circumstance, and we would say that--this is again just a speculation--but if we had a xenograft where we had confidence that lack of activity in the xenograft would correlate with lack of activity in the clinical circumstance, then, we might raise that as a possibility.

DR. MURPHY: A xenograft is one tumor, Steve.

DR. HIRSCHFELD: We recognize that, but I raise it as a possibility, and this is speculation.

DR. SANTANA: Donna, you have had your hand up for a while.

DR. PRZEPIORKA: I wanted to agree totally with Dr. Reynolds' comments that for non-targeted therapies, that we should be as inclusive as possible until we prove otherwise independent of the dialogue that needs to take place regarding priorities.

I would also like to agree with the fact that if we have a targeted therapy, it should be targeted towards patients in both populations who have that target, but I think Dr. Hirschfeld just made a very good point, and I was very happy that he said that, because this is one of the questions that I wanted to raise, and that is, what happens if there is in vitro data that suggests that it is not effective, and I think Dr. Poplack pointed out that, you know, breakpoints, everybody is talking about breakpoints, but, in fact, beyond the breakpoints cytogenetically, molecularly, there may be differences.

So, 9;22s may look different in ALLs in adults or pediatric patients if you go and look at the size of the protein, and with very specific targeted tyrosine kinase inhibitors nowadays, one

of those tyrosine kinase inhibitors may inhibit one of those tyrosine kinases, but not the other, despite the fact that the breakpoint looks the same.

So, I am happy to hear that the FDA would accept in vitro data to show that, hey, our drug isn't going to work in this pediatric population, let's not do the clinical study.

DR. HIRSCHFELD: I wouldn't quite go so far as to say the FDA will accept. I just wanted to raise the possibility as to another approach to the issue. For all we know, there might be some matrix hybridization schema that would evolve sometime in the fairly immediate future that we could have confidence in.

So, I wouldn't want to close the door on that.

DR. SANTANA: Dr. Schiffer.

DR. SCHIFFER: It is going to take a lot to destroy empiricism in oncology, and actually that is probably okay, because a lot of very important observations came out as a consequence.

Back to this mandate business, I am new to thinking about drugs and pediatrics, so excuse me if I step in it, but if we have a drug that is

active in relapsed AML, a traditional cytotoxic drug, but you are not allowed to test it or you are late to the plate because you are unable to do the Phase I trials until there is an adult dose, the second that drug shows activity, that is going to be the priority drug for pediatricians and adults with AML.

So, it seems to me that the problem or the issue is not whether you mandate those trials, the pediatricians would be dumb--and they are not--to pick up something immediately that has been shown to be active in adult disease.

It seems to me the issue goes back to how early the drug can be or rapidly the drug could be applied to children, and that is more a consequence of dose, and I guess I really hadn't thought about this 80 percent issue, and you need the adult dose to start in kids, et cetera, but it seems to me that for traditional cytotoxics, and maybe even biologics, that is something that needs a focus.

DR. SANTANA: Dr. Reynolds.

DR. REYNOLDS: One thing in this discussion I haven't heard is the interactions with the cooperative group, and we now have one national cooperative group for pediatric oncology. The

Developmental Therapeutics Committee within that cooperative group is very committed to interactions with each of the disease committees, so for AML or neuroblastoma, or any of these, there are liaison people between those groups.

It would seem that in the case of the FDA, where they are trying to decide whether or not to apply the Pediatric Rule versus the questions that have been raised like Dr. Arceci's, well, how early should we do this, and questions raised by Dr. Weiner about whether or not children should be at risk for doing this study, that maybe a dialogue between FDA and Developmental Therapeutics and the cooperative group would serve to provide some guidance for this.

DR. PAZDUR: We are all for dialogue, and as we developed in the exclusivity aspects, interactions between industry, the NCI, and Pediatric Cooperative Group.

One point that is a very practical point that I must emphasize, though, although this dialogue can occur, and there could be a dialogue about what agents should be selected, it has to be a fair and level playing field for all of the sponsors, in other words, we can't just select,

well, this drug, because the pediatric oncology community thinks it is hot, we will exert the Pediatric Rule in.

There has to be some overlying general principles that we could apply to the industry because it has to be perceived as fair and equitable to all sponsors.

DR. SANTANA: Sharon.

DR. MURPHY: Just to amplify the point, Pat, and for those who may not know, I mean I think there is, in the new Children's Oncology Group, already a mechanism, a platform by which the dialogue can take place, and it already has taken place.

There has been formed an industry advisory group, some members of which are here in the audience, that meet regularly with cooperative group investigators who are in the same room with FDA and NCI, so this is already a forum.

It can be used to facilitate the kind of dialogue that everyone wants to have, and it will, I am sure, and I hope later, some of the--I mean this is formalized already, so it is going to happen, but the point is, well, how are we going to make sure that it isn't just emotional or trendy or

some other kind of thing. We have got to have some kind of framework on which to move these discussions forward to prioritize.

DR. SANTANA: I want to get back to the questions. Is that okay, Dr. Hirschfeld?

DR. HIRSCHFELD: I was going to say Part C, I think we have discussed that.

DR. SANTANA: I was going to say, Part C, we have discredited the FAB, so we would all say that for APL, probably that is okay, but we have discredited B already, so there is no reason to discuss that.

For the chronic leukemias, do you want any comments on those specifically for Ph-positive CML? Anybody in the audience, Bob Arceci, or anybody else?

DR. ARCECI: I think as several people have already echoed, it is 9;22 and CML, they are so similar. It is the host that really matters in that situation, I think, but not the target.

DR. SANTANA: Lastly, are there any pediatric myeloid leukemias that have an adult counterpart that is not commonly classified as an adult leukemia? I would like to clarify that question, I didn't understand it when I read it.

Can somebody from the FDA help me with it?

DR. HIRSCHFELD: I could try to clarify that.

DR. SANTANA: What are you wanting?

DR. HIRSCHFELD: Sometimes or at least we could conceive of a circumstance where there might be a target. We will make something up, but we will say a particular receptor that is absolutely critical for a malignancy to maintain its phenotype.

There could be, at least in theory, a circumstance where there is not an adult counterpart, that is a leukemia, but the adult counterpart might be a solid tumor, it might be a lung tumor, it might be a breast tumor, it might be something else, and so we just wanted to raise the question, turning it around, is there some other tumor that if let's say we get an application that comes in for small-cell lung cancer, and we should immediately say, well, children don't get lung cancer, but there is a disease that is similar, which manifests in the bone marrow, or a histiocytosis, or something of that effect.

DR. SANTANA: Help me clarify, either you or Richard can help me clarify, I thought the FDA

gave approvals based on specific indications, and not broad indications. You help me with this. I don't understand how the agency in its current structure would say we are approving this drug for anything that expresses Y.

DR. HIRSCHFELD: Right, but the FDA has, and I think our trend is to approve or define an indication or describe the indication in terms which are fairly specific. So, it might be anatomic, and it potentially even could be histologically independent. It might be tumors--and this we haven't done, but it's a hypothetical--tumors that have a particular expression pattern or tumors that have a particular lesion, and that is how an indication in the future--

DR. SANTANA: But the problem there is how does that relate to the actual tumorigenesis, and it may be completely irrelevant.

DR. HIRSCHFELD: It could be, and then if that is the comment, then, that is the comment, but we wanted to raise the issue.

DR. ARCECI: I think it is a fascinating question in a way because there may be, in fact, some developmentally expressed genes that are going

to be quite unique to the pediatric setting. I can't think of many right now, but I think possibly one is--Charlie, you have to correct me on this in terms of the work in adults--but, for instance, the elastase mutations that are contributory to congenital neutropenias, that may contribute also to AML, may be a target that is really quite unique in pediatrics.

DR. SANTANA: I was thinking of the ATM story.

DR. ARCECI: ATM is potentially another, Fanconi anemia. There are some lesions that may be, in fact, very unique to the pediatric situation.

DR. SANTANA: Charlie.

DR. SCHIFFER: I don't think you need the FDA for that. I think that is where clever clinicians and clever doctors come in. You have the example of the patient who discovered for herself or himself about the c-kit mutations in GISTs.

DR. PAZDUR: I think that would have been probably very hard probably to mandate.

DR. SCHIFFER: Well, that is exactly the point. I don't think it is necessary to mandate.

I think the progress will happen.

DR. PAZDUR: The indication is the population, to answer your question, that is studied in the clinical trials in general, and I think that if we would--don't forget this is a mandate, okay, as I mentioned before, that we are requiring people to do this.

That link has to be well made and scientifically based and accepted by the scientific community, and I think that that is an underlying principle. It is not just, well, this is an interesting phenomena that may be an epiphenomena, how really intricate is it in the pathogenesis, because in essence what we are doing here is redefining a disease and how we define a disease.

DR. SANTANA: Steve.

DR. HIRSCHFELD: I would just would want to before we have our lunch break, make one point about the timing of the triggering of the Pediatric Rule, and that is in the lifetime of the development of a therapeutic.

The timing of the Pediatric Rule would be essentially near or at the time of NDA filing, so we already know that there is sufficient data in someone's mind to potentially register the product

for either a new molecular entity or for a new use.

We would presumably have some body of data, and it would be at this time that we would ask the question, well, should your data support pediatric use, and it wouldn't be necessarily earlier in the development.

DR. POPLACK: Just one comment. I particularly find intriguing this last discussion about having similar targets and the indication being, in that case, the target, and I think that is a very, very important concept here that we can't lose sight of.

DR. SANTANA: Thinking outside the box.

DR. POPLACK: We have to think outside the box, and not think about histological similarities, and I really think it is a very important point you raise.

DR. SANTANA: But I think the issue is what Richard said, that has to be scientifically validated to make it real.

DR. PAZDUR: Mandate obviously.

DR. POPLACK: Malcolm was mentioning track expression, for example, in lung cancer and neuroblastoma, and there are probably other examples, but the leukemia ones are evading us for

the moment.

DR. SANTANA: Susan.

DR. WEINER: I just didn't want us to lose the notion given who has gathered here today, lose the notion that we do need a platform for making these decisions. The notion of scientific community is very vague.

The notion of how this is going to get done and how these priorities are going to get set, either through the COG or through some interaction. Obviously, it has to be a multiple interaction, and we have to go ahead at some point, perhaps not in this forum, but those recommendations have to be made.

DR. SANTANA: I think we have tried to answer your questions and giving you the advice we were going to give you this morning, so we will adjourn for lunch, and we will reconvene at 12:30.

[Whereupon, at 12:00 noon, the proceedings were recessed, to be resumed at 12:30 p.m.]

AFTERNOON PROCEEDINGS

[12:40 p.m.]

DR. SANTANA: Let's go ahead and reconvene. There were three individuals that joined us after we had done the introductions this morning. For the record, we need to have those individuals introduce themselves - Dr. Friedman, Dr. Borowitz and Nancy Keene. Please state your name and your affiliation into one of the microphones for the record, please.

DR. FRIEDMAN: I am Henry Friedman. I am from Duke.

DR. BOROWITZ: I am Mike Borowitz from the Department of Pathology at Johns Hopkins.

DR. KEENE: I am Nancy Keene. I am one of the patient advocates on the committee.

DR. SANTANA: Thank you. Anybody else join us? I think that everyone else was here this morning.

Let's go ahead and start the afternoon session. This afternoon, we are going to follow the same format. We are going to have two presentations followed by a series of questions and then there will be a summary comment at the end from Dr. Arceci later this afternoon.

Open Public Hearing

DR. SANTANA: As required, we have an open public hearing, a time allotment. Is there anybody in the audience that wishes to address the committee? If you wish to do so, please state your name into the microphone in the middle of the room.

[No response.]

DR. SANTANA: If there is nobody who wants to make a public statement, we will go ahead and get started with this session.

DR. HIRSCHFELD: As you may tell by the fact I am in uniform, I belong to a team, and in this case the organization of this particular meeting is a result of a team, and I wanted to acknowledge and thank the members of that team, and I will begin with our division director, Dr. Richard Pazdur. Our team leaders, Dr. Allison Martin, Dr. Donna Griebel, and Dr. Grant Williams, and in absentia, Dr. John Johnson, and the other pediatric colleagues at the FDA, Dr. Ramsey Dagger, Dr. Al Shapiro, Dr. Joe Gootenberg, Dr. Karen Weiss.

Without their efforts, we wouldn't have the quality meeting that we have today. Thank you.

DR. SANTANA: Thanks, Steve.

So, let's get started with the Perspective on Lymphoid Leukemias, Dr. Borowitz, please.

Perspectives on Lymphoid Leukemias

Michael J. Borowitz, M.D.

DR. BOROWITZ: I would like to start this afternoon off with a not very extensive discussion about classification, and really sort of slant the overall classification of lymphoid leukemias heavily towards the issues at hand, namely, pediatric leukemia.

I don't propose this as any kind of an official classification, but just a framework for the discussion for today.

[Slide.]

Basically, in the broadest sense, lymphoid leukemia can be divided into acute and chronic. In the case of pediatric leukemia, obviously, it is heavily weighted towards the acute lymphoid leukemias, which are divided into three important groups, one derived from a precursor B cell, as we heard before, and that that is further subdivided, as we will see, and has already been alluded to by many speakers, completely in parallel to the situation in myeloid leukemia, it is further subdivided on the basis of specific molecular

abnormalities.

Precursor T-ALL is a little bit more controversial, how or if to subdivide that, but I think most people would still, from a biological perspective, separate that out from the larger group of precursor B-ALL, and then there is a special case of Burkitt's leukemia, which we will come back to again, and other speakers will deal with when talking about the lymphomas, because Burkitt's leukemia and Burkitt's lymphoma are really the same disease.

The chronic lymphoid leukemias in children we can dispense with the most quickly. There is, for our purposes, you don't even have to subdivide this, because these things don't really occur in childhood, but I have put down CLL and a whole variety of others.

[Slide.]

I think the one point I will make, and then we will dismiss this, is that for all intents and purposes, CLL doesn't occur in children, and I have run a reference laboratory, as many of you know, for many years and gotten leukemic samples from the Cooperative Oncology Groups and seen more than 5,000 cases, and of the cases sent to my

reference lab, have actually seen two cases of CLL, so I don't think we have to--if there were ever an orphan disease, CLL in children I think would qualify.

There are a few other chronic lymphoproliferative disorders and maybe some of those will come up in the context of the lymphomas, but again these are all rare.

[Slide.]

So, let's turn our attention to acute lymphoid leukemia and talk about the important entities. I think in precursor B-ALL, everyone recognizes that the four major translocations account for, in aggregate, about 40 percent of cases of childhood ALL, and these include the 9;22, those involving the MLL gene most commonly with AF-4 on chromosome 4 is the partner oncogene, but with others, as well, the t(1;19) and the t(12;21), as have been alluded to before.

A subgroup of ALL that hasn't been talked about much because even though it has been around a long time, and its prognostic significance has been known a long time, we really don't understand the mechanism of this leukemia or what the reason for its prognostic significance is, but that is

hyperdiploid ALL, and there is a growing awareness that it is not just simple hyperdiploidy, but, in fact, the specific chromosomes that are duplicated that seem to be most important in determining the prognosis in this lesion, and I think we can discuss that more if there is interest, but I don't think for purposes of today's discussion that that is necessarily a track which we have to go down.

Then, hypodiploidy, by contrast, clearly must have a very different mechanism of leukemogenesis, and does carry with it in everybody's series, a particularly poor prognosis, and is sorted out, but is a very rare group of ALL.

On the other side, precursor T-ALL, as we saw from I guess it was Sharon's slides, about cytogenetic abnormalities in T-lymphoblastic lymphoma, which is really the other side of the same coin, have a lot of different oncogenes involved, and in contrast to the model of precursor B-ALL, where most of these translocations involve production of specific fusion proteins which contribute to the leukemic phenotype, in T-ALL, the mechanism of leukemogenesis seems to be different in that it involves up-regulation of normal cellular oncogenes either by translocation to the

T-cell receptor, locus, or by other mechanisms that we don't know, and certainly many cases of T-ALL have abnormal expression of many oncogenes even in the absence of demonstrable translocations.

The important ones are SCL1 or TAL, HOX11, and probably LYL1 and the LMO1 and 2, in particular, are involved in a lot of translocations, but their role in producing leukemogenesis is a little less clear.

There is starting to be some emerging suggestion that maybe some of these have different prognoses, but I think those data are all pretty premature at this stage.

I have put down at the bottom of the slide as a separate category the idea of a primitive T-ALL, and this is a bias of mine that is supported a little bit by the data in the literature, but it is more anecdotal than anything else, and that is that people have divided T-ALL for a long time on the basis of expression of different kinds of differentiation antigens in the hope that this would be very revealing for the underlying biology.

In general, that has not been a very fruitful exercise with one exception, and that is that there seem to be cases of what we call T-cell

ALL that express very little in the way of markers that clearly indicate T-cell differentiation, and seem to share some properties in many cases with myeloid leukemias.

It is my own bias that the home for these leukemias may not be within the greater confines of what we call T-ALL, but this is still an emerging area.

[Slide.]

To sort of get to the essential points here, and that is what we were asked for, what are the differences between adult and childhood ALL, I think T-ALL is in some ways the hardest to deal with, and in some ways the easiest to deal with.

It is the hardest to deal with because there really aren't really good data on frequency differences among genetically defined groups. There is cytogenetic data that compares T-ALL in adults and children, but as I said before, it is not always the cytogenetic abnormality that drives the molecular abnormality, and we really don't know to what extent these things are the same, but again there is really not any good data that any of these genetically defined groups represent drastically different diseases in terms of the phenotype as

dictated by the patient outcome.

I think if we start getting to issues of drug targeting for particular molecular abnormalities in T-cell disease, we will have to start to revisit these questions, and there really aren't a lot of good data.

But I think that for current purposes I would submit that T-ALL in adults and children in aggregate are likely the same disease. Whether in the end there will be more children that use HOX11 and more adults that use SCL TAL, I don't know, but I don't think those data are at hand.

The other thing is that the frequency of T-ALL overall seems to be higher in adults than children, but that is really a false elevation because it has to do with the fact, as we will see in a second, that some of the most common kinds of B-precursor ALL are not found in adults.

[Slide.]

So, let's turn to precursor B-ALL, where there are more data and more ways of thinking about this. If you look at the cytogenetic abnormalities that we talked about before, and you look at the sort of comparative frequencies, the one thing that stands out is that BCR-ABL-associated ALL, the

single most common translocation in adult ALL, and it is a rare lesion, a relatively rare lesion in children, seen in about 4 percent of cases.

By contrast, the single most common cytogenetic translocation in children, the TEL-AML1 translocation, is a very rare lesion in adults.

So, to some extent, the difference between, if you would step back 2,000 feet, the biggest difference between ALL in adults and children is that in adults, they have a lot of Ph-positive or BCR-ABL ALL, in children, have a lot of TEL-AML1 ALL.

If I skip down to the bottom, you will see that hyperdiploid ALL also shows this relative increased incidence in children compared to adults, although it has been reported in adulthood.

The other translocations, E2A-PBX1 and MLL translocations seem to be a little bit different between adults and children, but probably not significantly so, and when you sort of take into account the distribution of other lesions, those numbers really aren't that different.

[Slide.]

So, the important thing is that these in children, is that these genetically defined lesions

in B precursor ALL carry with them important prognostic significance. The most important of these is the hyperdiploidy, particularly those involving chromosomes 4, 10, and 17, and the TEL-AML1 are associated with very good prognosis. Remember, those lesions are found with very low frequency in adults

By contract, BCR-ABL ALL and to a lesser extent the MLL-associated ALLs are associated with a poor prognosis, and again those diseases, particularly BCR-ABL, are more common in adults.

Finally, the E2A-PBX1, now with current therapy, although that used to be considered a poor prognosis lesion, with current therapy I think it carries the prognosis of any other standard risk child with ALL or high risk depending upon the clinical features.

Then, I don't want to underemphasize the fact that we have still only accounted for about 60 percent of children with ALL with all of these abnormalities, and there is a whole group of cases out there that we have not yet characterized. We know they have recurring cytogenetic lesions in some cases, but we don't really understand much about the underlying mechanism.

[Slide.]

So if I were to just summarize the important points here, first is that the good prognosis genetic lesions that are so characteristic of children, the TEL-AML1 and the hyperdiploidy, are rare lesions in adults and, for all intents and purposes, I think should be considered different diseases.

I think because they are good prognosis lesions, they are less likely to be targets of new therapy. The great majority of these patients are cured with conventional therapy, and in some sense, when you think about talking about treating children with ALL, or being experimental protocols, you are not talking about treating these children anyway, because we have excellent therapy for this group of diseases.

On the other hand, I would submit that there are really no significant differences between adult or childhood Burkitt's leukemia, adult or childhood T-ALL, or adult or childhood with BCR-ABL or MLL abnormalities, so that any protocols targeting these diseases are fair game for both children and adults.

This leaves the remaining 40 percent of

childhood precursor B-ALL. As far as we know, and this hasn't been investigated in detail, we can't pull out, once we take all the kinds of leukemias where we know the underlying molecular abnormalities, we can't discern any biological difference between adults and children with ALL once you take out all of these other abnormalities I mentioned above, but the important thing is that children still fare better.

And we really don't have a good handle on why that is, whether it has to do with differences in the host or, as Sharon Murphy said, differences in the doctors, but I think that is an important point as we think about targeting therapies to ALL not otherwise specified, we have to take in mind the fact that in contrast to AML, where children and adults fare equally poorly, in ALL, we are talking about this group of diseases where children still fare very well.

The other thing that I don't have on my slide, that I sort of want to say, is that another kind of ALL that we sort of don't think about in classification is relapsed ALL. Relapsed ALL, if you sort of step back a little bit, is the fourth most common cancer in children because even though

we do very well in treating children with ALL, the frequency of ALL compared to other diseases is so high that there is still a significant number of patients who relapse.

I think that we don't have a good handle. Relapses occur in every group including the best prognostic group, and I don't think we have a handle on the biology of relapse per se, and I think as we go forward, thinking about the biology of relapse as a way of thinking about targeting drug therapy, may be a more fruitful approach even than breaking it down by these lesions.

That is all I have to say.

DR. SANTANA: Thanks, Mike.

I am going to go ahead and ask Dr. Schiffer to do his presentation, and then we will have plenty of time for discussion.

DR. SCHIFFER: It will take a minute to rearrange these slides.

DR. HIRSCHFELD: I have one more public comment, and that is I wanted to acknowledge the professionalism and assistance that Karen Somers has given to this committee and to everyone else who had to make arrangements or to work out any logistical details, so thank you, Karen.

DR. POPLACK: Can we ask questions while we are waiting?

DR. SANTANA: Yes, go ahead.

DR. POPLACK: Michael, one of the things I find curious is that the concept of thinking about relapse ALL as one group, regardless of the unique biologies of these, seems to be going in a backwards direction rather than in a forwards direction.

It is ignoring what we now know and have the potential to know about the biological characteristics of these patients, so why choose to lump them and specifically for the purposes of this meeting where we are looking for indications, of what value is that?

DR. BOROWITZ: I will answer that in two ways. First, in the second practical way, if I had a patient who was good prognosis ALL by all hyperdiploid with all the favorable trisomies, and yet that patient relapsed, that patient is no longer a good prognosis ALL that is manifest.

So, I don't want to label that patient just on the basis of their favorable cytogenetics as a good prognosis lesion. Clearly, something has happened to that patient that has overcome the

otherwise good prognosis biology.

The issue of what that might be, I don't know, but I do know, for example, that an approach to some of the newer biologic studies with some of the DNA microarray data, for example, or other things, are to try to look for features that distinguish, given a particular genetic abnormality, patients who relapse from patients who don't relapse.

If, across genetic abnormalities, one can find some common threads, then, it may be that it is worth putting those together. On the other hand, it may be that the patient with TEL-AML1, who relapses, relapses for a different reason than somebody with Ph.

As of yet, we just don't know. All I am saying is that because we don't know, we shouldn't just shut our eyes to the notion of, well, you know, everything there is to know, we know from upfront genetic characterization.

DR. POPLACK: I agree with you 100 percent, we have to look harder in that group, but I don't know what the value is of lumping them at that point.

I think those are the patients that have

the clues to why we are not curing 100 percent, we have to look harder for more information, genetic or molecular, rather than just put them into one group. I guess I misunderstood what you were getting at with the concept of putting them all together as relapse.

DR. SANTANA: Any other comments?

Are you ready Dr. Schiffer?

DR. SCHIFFER: Yes, I am ready.

DR. SANTANA: Okay.

Charles Schiffer, M.D.

DR. SCHIFFER: I am finding it a challenge to say something new, that hasn't been said already. I don't know whether I will say it differently, probably worse, but there are a number of points I think perhaps still to be made.

[Slide.]

There are differences between adults and children. We see an awful lot of this, you don't see it at all maybe except if you look in the mirror every once in a while, but this represents an enormous challenge to those of us treating hematologic disorders in adults and--I had a slide of a child, but you get the point.

[Slide.]

Mike talked about this already. The biologic differences and similarities, we have stated. There is a profound difference in the incidence of TEL-AML in adults and children and hyperdiploidy. In fact, I think that estimate of 5 to 10 percent of adults being hyperdiploid is very high. It is much higher than we just published in the CLTB where it didn't even show up in the listing of cytogenetic abnormalities in 200 patients with ALL, and, of course, the bete noire of the Philadelphia chromosome.

The frequency in probably the impact of the MLL and the mutations are probably the same in adults and children, and we can talk a little bit more about that when we talk about Burkitt's lymphoma and why we do well with adults, but not quite as well as you all seem to do.

These are incredibly rare in adults, that is, hypodiploidy and 1;19, well less than 1 percent of patients, but I would agree with Mike's comments that, in fact, you can extrapolate these discrete abnormalities just as we said in AML from adults to children for the purposes of this discussion.

[Slide.]

There are obvious differences in adults

and children and even young adults, and we can't ignore it. Adults have other medical conditions, and a lot of those are subclinical and we haven't the foggiest idea of what that does in terms of drug disposition, very subtle abnormalities of hepatic, cardiac, or renal function, and all the clinical trials that are ever submitted to the FDA don't have real adults, that is, they have perfectly well patients with cancer, and that is not what we see in the clinic as soon as a drug is approved.

Children remind me of those little toys, you know, where you bang it up and down and they keep coming back, well, you can't do that to adults. It is very difficult to give intensive repetitive courses of therapy to adults. It is not just L-asparaginase, it's high-dose methotrexate, it's high-dose ara-C, it's stuff that causes mucositis.

Adults are much less physically, and perhaps even emotionally, less tolerant, and while we would love to have a focus on long-term toxicities in adults, unfortunately, that is rarely our problem, but it is a very major problem in pediatric oncology.

But this whole issue of extrapolating dose from adults to children is, of course, problematic, and we have alluded to it, but in general, children can tolerate much higher doses of drugs than can adults, and we face this question at times in adult oncology.

[Slide.]

In the STI studies, everyone gets the same dose. This is the NBA playoffs - so we give Shaquille O'Neal and Mugsy Bogues the same dose simply because they are 18 or 21, however old you have to be to vote, and obviously, the extrapolation to children is there.

I notice actually in the Phase I studies that are being done with STI in children, it is being somewhat more rationally dosed on a mean square basis rather than the same dose for everyone. It turns out for a biologic agent like this, fortunately, the dose that was chosen exceeds the therapeutic threshold in both Shaquille and Mugsy, but that is not going to commonly happen with anti-neoplastic therapy.

[Slide.]

These are the results you see in adults, all comers with ALL. It is very age dependent. In

the 20 percent of people who are this old, there are very, very few cures, and that is predominantly because they are almost all Philadelphia positive. If you break it down even further, this largely reflects the incidence of Philadelphia chromosome positivity.

The same issues with regard to T and B lineage ALL. These are the Ts. They used to be our worse group and now our best group as a consequence of intensification of therapy, actually based on some of the pediatric models, but still not as good as you all do, and no understanding, as Michael said, of whether the different genetic subtypes offer an advantage or a disadvantage.

These all the BCR-ABLs and the 411s, and most of those people have been transplanted. That is how they got out there. Very few survive without transplant.

This is that very difficult group that I think deserves some discussion, as Michael said, of the other Bs, do half as well at the most as you all do in pediatrics.

[Slide.]

Now, what are some of the possible differences and can we do trials together? Well,

there was this very disturbing abstract that was presented at the American Society of Hematology, which should have been on the plenary session, but wasn't, which represented the CCG and CALGB, comparing the outcome in adolescents and young adults with ALL treated either on pediatric or adult protocols.

[Slide.]

196 adolescents, 103 treated by CALGB, approximately the same time period. Interestingly, they are identical CR rates, and I will get back to why I think that may be important, but a little more than half the event free survival in patients treated on the adult protocol by adult oncologists.

[Slide.]

What are some of the reasons? Probably not risk factors. The groups were reasonably well balanced, the adults were a little bit worse. This may account for about 5 percent of the difference.

The regimens are different, the pediatric regimens were more asparagine intense, but I will say that we designed the CALGB regimen attempting to take the most intensive of what were the extant pediatric regimens at that time and tried to apply them to adults.

So, I am not certain how much difference there was in the regimens. That remains to be looked at. We haven't the foggiest idea, however, about the doses delivered. We know the doses delivered in induction, that is easy. People are in the hospital, you read the protocol, you give them the drugs, but the ALL regimens are very, very complicated. They have very tight schedules, which may or may not be necessary, but they are written as such, and we haven't the slightest idea of the drug delivery rate or total drug given by pediatricians versus adults.

But there is a very big difference. All of the people treated in the CCG studies were treated by people who do ALL for a living, it's their bread and butter, they do nothing else. They don't have to look at the protocols, they have got it memorized. The nature of adult oncology is different.

I am not certain what percentage of these adolescents were treated in cancer centers or transplant centers where there were people who were devoted to leukemia as opposed to being treated in the community by doctors who are more general oncologists and they do colon and breast and lung

at the same time, and it may very well be that it is not necessarily the doctors, but the type of doctors who are delivering the care to this type of patient.

I must say we have seen the same thing or I have seen the same thing in evaluating patients treated with interferon for CML in the STI studies or I have seen sometimes rather bizarre patterns of care generally administered by people who were not hematologic oncologists, so not all the patients who you see treated in that comparative study, which is really very, very important, were treated by hematologic oncologists.

Many were treated by more general medical oncologists, and I think these data need a lot more digging into to see what the real cause of those various differences are, and it may also have some implications with regard to doing parallel trials in subgroups of patients with ALL.

I don't think it pertains as much to AML. AML is sort of easy. Things are in blocks, and you do it, and adults are pretty good at that, adult oncologists. ALL just might be very, very different.

[Slide.]

Now, what about the types of agents that we might be talking about, comparing adults and children? The stuff on the top I think is pretty straightforward. The next STI or the next highly targeted antisense will have a target which I think we have a consensus should be applied to both adults and children if that target is there.

The same thing might apply to antibodies, such as anti-CD33 or the next one that comes along as long as the cell expresses that antigen in an adequate enough fashion.

There are going to be two different types of cytotoxics, some that may have a little bit of specificity if it turns out to be true of this 506U for T lineage ALL, and one might imagine, although there are toxicity differences again between adults and children, that the results might be extrapolated from one group to the other.

We have already talked about what I call plain old new drugs. That is simply because many new drugs are variations, unfortunately, on old drugs, and there aren't too many new, new drugs.

There are also issues in leukemia with regards to supportive care, that is, myeloid cytokines to attenuate neutropenia, et cetera, were

studied predominantly, if not exclusively, in adults first, and then children, and they may be very different because the intensity of the regimens are different and the cardioprotectants, which are much, much more of an issue in children, were actually studied backwards, because it is not a public health hazard in adults whereas, it may very well be dose and life-limiting n children, and then there is this whole other group of compounds, anti-angiogenesis I just list as one possibility, which are broad and may not be as specific and probably should be studied, I think differently in adults and children perhaps.

[Slide.]

Lastly, I was struck in listening to the conversations about pediatrics about how this--with children--this is parallel to thoughts I have been having about what happens with the next STI and how do you develop that. I have been involved in those trials, found it to be one of the most exciting things I have ever done, and like everybody, I am looking forward to the next one.

But the question is that these are very rare disorders. CML is pretty uncommon, but has a high prevalence because people live five, six,

seven years, but t(8;21s) and MLLs, and all that, are very, very uncommon diseases even if you pool adults, children, and adolescents, and it is not clear what the stimulus for pharmaceutical companies will be to develop things that are so highly targeted, but on the other hand, this is the major goal of what we are hoping to get out of all of this fancy molecular biology, that is, small molecules.

We have the example of STI that are going to discretely target these lesions which are obviously critical to many of these diseases, but how is our society going to provide an inducement for the large expenses that are necessary to develop such molecules?

I think we need some creative thinking between government and between the pharmaceutical industry to figure out models for how this can be done expeditiously because obviously, this is the kind of therapies that we want out of all the science that we are paying for.

I think I will stop there without an answer certainly to this.

DR. SANTANA: Thanks, Dr. Schiffer.

Since there was a request for public

hearing, is there anybody in the audience that wishes to address the committee? Please come to the microphone in the middle, state your name and affiliation.

Open Public Hearing

DR. RACKOFF: Wayne Rackoff from Ortho Biotech Oncology. I am speaking today on behalf of, one, my colleagues on the COG Industry Relations Committee, Raj Malik and Alan Malamud, Raj from BMS and Alan from Lilly.

Just to respond to some of the comments this morning and our meeting just this past Saturday, first of all, the COG Industry Relations Committee has been constituted to try and get at just some of the issues that have been discussed today. I know Malcolm Smith has participated, Rich Pazdur and Steve Hirschfeld have both participated, as have some other members of the panel.

In discussing this over lunch, which is why we were late, when you had the first call, we had to go outside the hotel, because you guys had the lunchroom closed off there, the Pediatric Rules had a couple of unintended effects, I think.

One is that there are now 12 premarketed agents in COG Phase I studies and 5 pending the

opening of protocols, and I think that is unprecedented just in my short history in pediatric oncology. The second is that there are probably at least that many pediatric oncologists working in industry. I don't think those two things are unrelated.

So, although the specifics of how the Pediatric Rule is going to be applied are still being discussed, I think the effects of the Pediatric Rule are already being manifest and really they are unintended effects.

The second is this timing issue, that the Pediatric Rule, no matter what happens, the way the law is written, the way it is has been interpreted, it does not affect timing as we understand it. In fact, if it does, it really affects it quite late in the game.

So, a number of the agents are being tested in pediatrics well prior to filings being prepared, and that is not going to be affected really by any of the discussions we have had today.

The third thing we talked about at lunch was the fact that although there is a lot of talk about targeting and targeted drug therapy, on the other side of the aisle, if you will, drugs are

being identified or molecules are being identified using these molecular targets, and they are being identified as lead candidates, but to cross the threshold from discovery into development in human trials, really, the drugs are being subjected to traditional screening against cells and xenografts.

So, what we might think of as a very targeted drug coming through the pipeline because it is targeted to geranyl geranylase may turn out once it is put into animals with various tumors, not to be working by the mechanism of action.

So, I think we would argue for a fair, level, sort of broader approach to thinking about these things in terms of diseases where therapy is similar in adults and children. Ara-C, we still don't know the exact mechanism for maybe not ara-C, but for prednisone in leukemia--David, you could correct me if I am wrong--but we still know that if it works in adult Hodgkin's disease, it is probably going to work in pediatric Hodgkin's disease.

So, those are just some thoughts in response to Sharon's request that we speak up a little bit, that we wanted to put out there from the industry perspective.

The one other thing that came up at lunch,

and really for the FDA to consider, is this idea of setting priorities. This is something we are working on in COG, and this is going to have to be a collaborative effort.

You know, there is liposomal doxorubicin, there is another doxorubicin, Doxil, there is doxorubicin, there is epirubicin, there is adriamycin, and do you put each--you know, you want to level the playing field, as Rich Pazdur said, but on the other hand, you don't want to take up all the patients in studies.

The final point, and this really comes mostly as a consumer, somebody who lost a brother to cancer, is that Malcolm Smith has been sort of the protector of kids over the years, maybe not Malcolm alone, but CTEP, in terms of looking at safety, so as we approach this timing issue, I think we really have to balance that against safety and appropriate medical need in terms of bringing these agents into children at a younger age.

DR. SANTANA: Appreciate your comments.

Anybody on the committee want to add further to that?

DR. RACKOFF: Did we cover all the Burger King conversation? Okay. If you are going to have

it in a hotel and close the restaurant, you have got to give us like 10 more minutes to get back.

DR. SANTANA: We didn't close the restaurant. We ate in here, a box lunch. Our lunch was boxed.

[Laughter.]

DR. SANTANA: Malcolm, do you have a comment?

Discussion

DR. SMITH: I will just say, one, on behalf of CTEP and I think on behalf of COG, as well, we certainly appreciated the efforts of the pharmaceutical companies who have been participating in the COG Pharmaceutical Committee, Industry Relations Committee.

The other, this would be a question to the FDA, it really has struck me that a number of these agents before they are approved, are being studied in children with cancer, and that, in fact, we are being relatively successful, at least in the recent 12 to 18 months, in doing this.

So, it would perhaps be interesting to compare the success at doing this in childhood cancer with some of the other situations that you are facing with exclusivity, how many of those are

pre-approval studies that are being done as opposed to marketed drug.

I think that is a tribute to a lot of people. You know, the efforts of the FDA, the pediatric oncologists who are working in the pharmaceutical sector now, the advocate community, the pediatric investigators who identify needs and advocate for children to have a particular drug tested.

So, you know, it is half full, half empty, but I think right now there are a number of very interesting agents that we have access to at a relatively early stage, and we keep working at that.

DR. HIRSCHFELD: I, first of all, appreciate Wayne Rackoff's comments and those of his colleagues that he was the spokesperson for, and in answer to the question that Dr. Smith raised, there are areas outside of oncology where drugs are being developed for children prior to approval in most of the therapeutic areas, but I think this is another case where oncology may be leading the field, and that the proportion of drugs which are being developed are drugs which are in the early stages of development.

There are relatively few, although there are some approved drugs which are being revisited or being developed in new paradigms for pediatrics.

DR. PAZDUR: I would just like to address two aspects, the first being selection of agents to go forward into clinical trials. I really think that that is not only a problem for pediatrics although it is more acute in pediatrics because of the limited patient resources.

It is also one that I think adult medical oncologists have to come to terms with, how many aromatase inhibitors do we need on the market, can we prioritize the development of drugs better in adult medical oncology, and that is one thing that we have, as an oncology community rather than just a regulatory agency, have to come into play with, because to take an agent to demonstrate clinical benefit, to get a drug approval is a very expensive process, and just because one has a drug, is it really going to make an impact, and perhaps there needs to be greater thinking on a national level in conjunction with the NCI, et cetera, of how to better utilize clinical trials' resources rather than it is there, therefore, we must develop it.

The other comment I want to address is Dr.

Schiffer's comment about changing paradigms for new drugs that come out in clinical development for them. Should we have different endpoints for drugs that have unique mechanisms?

As you know, for the approval of a drug, our major emphasis has been the demonstration of clinical benefit, and it is kind of a mantra in the regulatory agencies throughout the world, clinical benefit, clinical benefit, clinical benefit.

These usually require large trials. Why? Because many times the treatment effect is so, so minimal, you need large trials, large survival trials if you are trying to find a very small difference.

Hopefully, with relatively selective therapies, where you are actually selecting a target out, that will improve the response rates, the survival of a given population, so the treatment effect will be much greater, and therefore, enable us to still answer questions of clinical benefit with limited numbers of patients.

You know, if you are improving survival by 100 percent or 120 percent, that is going to be a much different population than by a 10 percent or a 20 percent difference in survival just based on

patient numbers.

So, I think, hopefully, you know, some of these questions will answer themselves. The question that we always have to grapple with because we are under a great pressure of it is should we change the approval criteria for drugs with unique mechanisms of actions, such as cytostatic agents, angiogenesis inhibitors.

So far, basically, we have kind of stated that clinical benefit is clinical benefit, and we really want to see these endpoints, but I think they need not be unattainable if these agents really are used in populations that are selective in a sense.

DR. SANTANA: Richard, can you further clarify for me because I thought in one of the regulations, particularly when you are extrapolating adult data, that the requirement was demonstration of activity in pediatric studies. To me, it is not a play of words, but to me, activity is very different from survival.

DR. HIRSCHFELD: I think you are referring to the principle, which was first enunciated in the 1994 Pediatric Rule, which says that in order to register a product for pediatric use, that if

certain conditions were met in terms of the disease having similarities between the adults and the children, and the mechanism of action of the drug having certain similarities, that there would be a decreased burden on demonstrating efficacy because it was felt and believed that you could extrapolate some of the efficacy data, and therefore, would just need to do the pharmacokinetic and some safety data.

In oncology, that has never been used, and in other arenas, it has rarely been used, so we look on it as an attempt which sounded like a good idea at the time, but hasn't proved to be practical.

DR. PAZDUR: What I was referring to by the clinical benefit basically is the initial approval of a molecular agent or new molecular entity or a supplemental approval in an adult indication, where they are usually having the initial approval rather than an extrapolation of data.

But I think that these are questions that we are continually grappling with, as well as the oncology community in general, because there is various steps in the development of an agent. It

is not only the identification of biological activity, number one, it is the selection of agents that one should take forward for further clinical development, which usually in adult medical oncology is a very muddy area. Number three, the actual demonstration of clinical benefit.

But once you start skipping around here between these three steps, it becomes problematic.

DR. GOOTENBERG: I just wanted to take the opportunity to make it clear that in biologics, we feel that we are going to have a lot of the novel mechanisms of the future, and that these questions are going to be even more compelling when we get to cellular therapies, gene therapies, and the more advanced cytokines.

DR. SCHIFFER: With regard to your comments, Rick, first, there certainly is precedent for approving home runs based on relatively modest data, and ATRA is an example, the hairy cell drugs are an example. It was pretty obvious what was going on, and I would assume that that is what you are referring to, and that that is going to happen in the future as we have more home runs.

DR. PAZDUR: We have no problem in using surrogate endpoints in a sense, but the point that

I was trying to get across, if you could select out a group of patients from, for example, the total denominator of lung cancer patients that was destined to have a good response to therapy, that effect is going to be so much greater, and the numbers of patients that you would need to answer that question is going to be so much less that these trials will be easier to do, and therefore, we necessarily don't have to go away from traditional endpoints although we are willing to look at different endpoints for different diseases.

DR. SCHIFFER: With regard to the prioritization issue, things are very different in children and adults. The children's group have all the patients, period. In adults, in fact, the Cooperative Groups do relatively few of what might be called licensing trials except as they get picked up by pharmaceutical companies in retrospect.

The large prospective trials, if a pharmaceutical company thinks there is money to be made with another aromatase inhibitor, are done by putting together these large ad-hoc groups of highly organized practitioners who do these trials very well, and actually, probably more rapid than

the Cooperative Groups. One reason that they don't go to the Adult Cooperative Groups sometimes is the absence of speed--

DR. PAZDUR: Or control.

DR. SCHIFFER: Or control--with which these things can get done, but with regard to prioritization, it is a totally different issue in pediatrics and adult oncology.

DR. SANTANA: Dr. Arceci.

DR. ARCECI: I would be curious to know, and I think, Malcolm, because of your role at CTEP, I would be curious to know your opinion, can we do surrogate marker endpoints in new agents for pediatric patients, is that a legitimate approach in a setting that is a little different than what we have done in the past? It may be okay, but I would be curious to know what people think.

DR. SMITH: What do you mean, give me an example of a study.

DR. ARCECI: Well, is it adequate to set up a study to look at the inhibition of farnesylation without a clinical endpoint, can we look at demethylation without necessarily a clinical endpoint being the priority in such a study? We have grappled with these questions, and

don't really have an answer.

DR. SMITH: I mean it is a real challenge. The studies that have been done in adults, for example, the current wave of anti-angiogenesis studies where you are getting samples before and after, perhaps multiple times during therapy, it is very difficult to do those in a pediatric population.

There are solutions that have been found, for example, Henry's studies with benzo guanine where a dose is determined in adults that affects the target sufficiently, the pharmacokinetics are understood in adults, and then the dose is identified in children that achieves those same levels of the drug.

So, there is an extrapolation there, but a reasonable extrapolation. The FTI studies, instead of using tumor tissue, might use buccal cells or another source of normal tissue as a surrogate endpoint to show that the target has been affected. Of course, it is easier to do surrogate endpoint studies in the leukemia population than in the solid tumor population, so those types of studies are possible, some solutions are possible, but there will be times when it is just very difficult